GlaxoWellcome

1826 '99 JUL 20 A11:18

July 19, 1999

Management Dockets
Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1-23
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket Number: 99D-0674

Dear Sirs:

Please find enclosed GlaxoWellcome's comments on the draft Guidance for Industry - INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry, Manufacturing, and Controls Content and Format.

Please feel free to call me at (919) 483-6408 if you need additional information or clarification regarding the comments.

Sincerely,

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Regulatory Affairs and Quality Division

99D-0674

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Comments from GlaxoWellcome on the Draft Guidance for Industry - INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products - Chemistry, Manufacturing, and Controls Content and Format

General Comments

We commend the Agency for its pragmatic approach in providing regulatory relief in the three specific areas outlined in lines 32–41 of the guidance. We are especially heartened by the Agency's recognition that, from a CMC standpoint, patient safety is paramount during the phase 2 and 3 clinical trials and only those information and data that may affect safety should be submitted as information amendments. We specifically support the following quotes from the draft guidance: "The sponsor may elect to delay submitting data elements obtained in earlier investigations until phase 3 if they do not affect safety," "The recommendations in this guidance on CMC information focus on safety issues relating to phase 2 and 3 studies," and "In general, CMC safety information and data and CMC safety updates should be submitted during IND clinical trials as information amendments."

Having said that, we feel that the document when discussing the data requirements for phase 2 and phase 3 occasionally confuses between the safety-related information that should be submitted in an information amendment and general information that should be collected during the IND phases. To resolve the confusion, we recommend that the guidance separate the safety information that should be submitted as an information amendment from the non-safety information that could be postponed until the end of phase 3 or submitted in summary annual reports. For example, under phase 2, Drug Substance, Synthesis/Method of Manufacture, lines 130–131 state "The structure of the starting materials and information to support the classification of a compound as a starting material should be provided...." This clearly is not safety-related information and may be postponed until the end of phase 3. Similar examples can be cited on lines 155–162, 166–176 and others through out the draft guidance.

We strongly recommend that 1) a tabular summary similar to the SUPAC guidances be included in the final guidance. Inclusion of information from phase 1 guidance in summary table would add to clarity and usefulness. 2) The information specific for biotechnology derived products should be separated from synthetic drugs or be more specifically identified.

Specific Comments

Phase 2

Lines 17- 20 - On line 17, the draft guidance includes specified biotechnology products as defined in 21CFR601.2, but on line 19 the document states that it does not apply to vaccines. Some of these specified biotechnology products are considered therapeutic vaccines. This appears to be contradictory and needs clarification.

Lines 32 - 41 - Examples of the types of changes that may affect safety would be useful for both synthetic drugs and specified biotechnology products. FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, April 1996 may be a useful model. Also, examples of the types of data and information that may be postponed for submission would add clarity.

Lines 72 - 73 - We recommend revising the sentence "If these data are not generated...they are generated during phase 3" as "If these data are not generated in phase 1 or phase 2, they should be generated during phase 3 and submitted in summary annual reports." The sentence as written in the guidance implies that information amendments should be submitted as the information is generated.

Lines 90 - 93 - Recommends the sponsor to discuss with the Agency the type of manufacturing data that should be submitted to support the safe use of the drug in all investigational phases. While it is a good idea in concept, this can also result in inconsistencies in requirements between reviewers and divisions. The sentence should be revised to state that this guidance is the primary source for such information for phase 2 and 3 and inputs from end of phase 2 meeting may supplement the information that may be needed during phase 3.

Lines 101 - 102 - We recommend deleting "...(1) updated Phase 1 information (see November 1995 phase 1 guidance, section IIIF) and (2)". This appears to contradictory to the General Principles on lines 66–88, which indicates safety issues need only be updated.

Drug Substance

Lines 120 - 121 - The draft guidance recommends submission of more detailed description of the configuration and chemical structure for complex organic compounds. This is not a safety issue and may be postponed until phase 3.

Lines 125 - 126 - We suggest inserting the words "in the summary annual report" after "identified" in the sentence.

Lines 130 - 133 - The draft guidance recommends submitting structure of starting materials and information to support the classification of a compound as a starting material. Firstly, it is too early to have fixed the synthetic pathway and the starting materials. Secondly, information on classification of the compounds as starting materials is not a safety issue. We recommend that the lines be revised to state that the impact of any new or changed starting materials should be evaluated for safety and the information submitted in an information amendment if the change may affect safety. Otherwise the information may be submitted in summary annual report."

Lines 141 - 142 - States "Safety updates on reagents, solvents, auxiliary materials, and proposed changes identified during phase 1 should be provided." It is unclear what safety updates on reagents, solvents and auxiliary materials are being sought. If these were safe in phase 1 then they should continue to be safe in phase 2. We suggest revising the sentence as "Any new reagents, solvents and auxiliary materials should be evaluated for safety and information submitted in an information amendment if the change may affect safety. Otherwise, the information may be submitted in summary annual report."

Lines 148 -153 - Synthesis methods are still evolving during phase 2. We recommend that first sentence be revised as "Any changes in the synthetic route and manufacturing process should be evaluated for safety and information submitted in an information amendment if the change may affect safety. Otherwise, the changes may be reported in summary annual report."

Submission requirement for the provisions for monitoring and controlling conditions in each step is excessive at this phase. We suggest deleting the last sentence, lines 151–153.

Lines 155 - 162 - This paragraph dealing with tentative acceptance criteria appears to confuse between general information that is collected during the IND phases and safety information that should be submitted in an information amendment. While this information is useful, it is not safety-related and may be submitted in summary annual report.

Lines 166 - 176 - Reference standards and establishment of a working standard is general information that is generated during the course of drug development. Again, this does not affect safety and the submission of this information may be postponed until phase 3.

Line 170 - 171 - States "A working standard is a reference material that has been further characterized beyond standard batch release." Examples of "further characterization" may be helpful.

Line 189 - The first sentence should be revised as "Any new tentative acceptance criteria or a relaxation of a tentative acceptance criteria should be reported in an information amendment if it may affect safety."

Line 192 - We recommend deleting the sentence "Any changes in the acceptance criteria should be stated." Revised line 189 makes this line redundant.

Lines 190-192 - During phase 2, the analytical methods are still evolving and validation of analytical methods are limited. We recommend replacing the phrase "supporting validation data should be available on request " with "appropriate validation data should be available on request".

Lines 193 - 194 - The sentence should be revised as "A summary table of the test results, analytical data of the clinical trial material prepared since the filing of the original IND should be provided in summary annual reports."

Lines 198 - 200 - The sentence should be revised as "A brief description of any changes in the immediate container closure systems should be provided in summary annual reports."

Line 204 - We recommend deleting "(or drug product)" in the first sentence.

Line 213- 215 - Inclusion of some examples of stress studies would be helpful. Perhaps stress study conditions described in ICHQ1A may be included here.

Line 220 - The sentence should be revised as "Stability data for clinical trial material used since phase 1 study should be updated in summary annual reports."

Drug Product

Line 234 - 235 - We recommend deleting the sentence "A batch formula should be provided, if not already submitted." In the course of clinical trials, many clinical trial batches of various batch sizes may be made due to availability of the drug substance or other development reasons. A batch formula in the context of varying clinical trial batch sizes is pointless.

Lines 235 - 237 - The expectation in the sentence "The formulation for certain drug products delivered by devices... should be similar to that intended for the marketed drug product" is impractical and premature. Formulations and device design and configurations are generally optimized during phase 2 based on the results from dose ranging studies and early efficacy studies. The sentence should be deleted.

Lines 241 - 242 - The first sentence should be revised as "Any new tentative acceptance criteria or a relaxation of a tentative acceptance criteria should be reported in an information amendment if it may affect safety."

Lines 246 - 247 - We recommend inserting the word "if available" at the end of the sentence "A brief description of ...provided (e.g., DMF, NDA, BLA)." The manufacturer of a totally new excipient may not have a DMF, NDA or a BLA in place this early in the development process. However, as long as the IND sponsor assures the safety of the excipient in the dosage form that should be adequate for phase 2.

Lines 253 - 254 - The sentence should be replaced with "The addition, deletion, or change in the drug product manufacturer reported in the original IND submission should be updated in the summary annual report."

Lines 258 - 265 - We recommend replacing the complete paragraph with "An updated brief description or a flow diagram of the manufacturing procedure should be provided if the procedure has changed since phase 1."

Line 276 - The first sentence should be revised as "Any new tentative acceptance criteria or a relaxation of a tentative acceptance criteria should be reported in an information amendment if it may affect safety."

Lines 281 - 282 - During phase 2, the analytical methods are still evolving and validation of analytical methods are limited. We recommend replacing "supporting validation data should be available on request " with "appropriate validation data should be available on request".

Lines 282 - 283 - The sentence "Any changes in...tests performed" may be deleted. Revised line 276 makes it redundant.

Lines 286 - 287 - We recommend revising the sentence as "A summary of the...in clinical trials should be provided" as "A summary of the test results of the drug product used in clinical trials should be provided in summary annual reports." Analytical data such as chromatograms are of limited value since the methods are still evolving. Also, the test results will be summarized in the table, submitting the COA is thus redundant.

Lines 291 - 292 - The first sentence should be revised as "A brief description of any changes in the immediate container closure systems should be provided in summary annual report." The clinical trial material may be packaged in various configurations to meet the trial design needs; this does not pose a safety risk.

Lines 303 - 305 - We recommend revising the sentence as "Stability data for clinical trial batches used since phase 1 study should be updated in summary annual reports."

Phase 3

It may be beneficial to reiterate and reinforce at the beginning of this section that the information and data under this section should be generated during the phase 3 studies and only that information which may affect patient safety should be submitted in an information amendment. Information other than safety may be submitted in summary annual reports.

Drug Substance

Lines 321 - 328 - The guidance should provide examples of characterization data expected for plasmid DNA products.

Lines 340 - 341 - We recommend substituting "available" for "provided" in the sentence.

Line 364 - We suggest deleting "the type of reaction vessel".

Line 366 - We recommend replacing "complete description of the analytical procedures" with "brief description of the analytical procedures".

Line 369 - We suggest that virus validation should also be included for specified biotechnology products.

Line 401 - Perhaps concepts from the ICHQ2 document may be included here.

Line 408 - The sentence "Suitable limits based on manufacturing experience should be established" should be revised as "Suitable tentative limits based on manufacturing experience and available stability data should be established." Even during phase 3, experience with the drug substance is limited and only tentative limits can be reasonably established. These limits may be tightened or relaxed based on additional experience in the NDA submission.

Lines 413 - 415 - The sentence should be revised as "A summary table of the test results, analytical data of the clinical trial material prepared since the filing of the original IND should be provided in summary annual reports." Data in the summary table will be abstracted from batch release data and COAs submitting these is redundant.

Line 433 - We suggest deleting "submitted" from the sentence. Also, "detailed description" of the drug substance in the sentence needs clarification.

Line 437 - 438 - We recommend inserting "Summary" at the beginning of the sentence "Tabulated data should...drug substance lot."

Lines 438 - 440 - The sentence "Each table should contain data from only one storage condition" should be deleted. We also recommend revising the sentence "Individual data points for each test should be reported" as "Individual data points and representative chromatograms should be available on request." Submitting individual data points and chromatograms does not add value.

Lines 442 - 446 - This paragraph should be deleted. The stability data should be self explanatory in demonstrating appropriate storage of the drug substance used in the clinical trials.

Line 467 - The word "tentative" should be inserted before "acceptance criteria..." in the sentence.

Lines 485 - 492 - We recommend replacing the complete paragraph with "An updated brief description or a flow diagram of the manufacturing procedure should be provided if the procedure has changed since phase 2. Reprocessing procedures and pertinent controls should also be described briefly, if applicable."

Line 508 - Perhaps concepts from ICHQ2 regarding methods validations may be included here.

Line 509 - 510 - The word "tentative" should be inserted before "acceptance criteria" in the sentence.

Lines 541- 542 - Dissolution profiling should be used in setting dissolution parameters and tentative acceptance criteria. This should be moved to the specifications section. Perhaps reference to the FDA's Guidance on Dissolution Testing of Immediate Release Dosage Forms may also be relevant.

Lines 548 - 549 - The sentence "Each table should contain data from only one storage condition" should be deleted. We also recommend revising the sentence "Individual data points for each test should be reported" as "Individual data points, representative chromatograms should be available on request."

Lines 552 - 556 - This paragraph should be deleted. The stability data should be self explanatory in demonstrating appropriate storage of the clinical trial batches.

Lines 558 - 562 - We agree with the concept for developing a container closure challenge test at this phase.

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